

Attorney Docket No.:
TLHR-0005 (124187.00009.US2)

REMARKS

Applicants have carefully considered the Examiner's Final Office Action, and respectfully request reconsideration of this Application in view of the above Amendment and the following remarks.

- (a) Claims 1-20 and 36 are claims the have been selected by the Applicants indicated in the restriction election requirement.
- (b) Pending in this Application are Claims 1, 4-6, 8-12, 15-20, 36, and 39; and
- (c) Claims 1, 4, 5, 6, 7, 8, 9, 10, 18, and 36 have been amended.
- (c) Claim 39 is new.
- (c) Claims 21-35, 37 and 38 have been withdrawn from further considerations as being drawn to a non-elected invention as indicated in the restriction election requirement;

Amendments to Claims:

The Amended claims find support throughout the specification, including the following sections:

Claim 1, 4, 5-10, 18, and 36

Page 5, lines 24-30; Page 10, lines 7-20; and
Page 11, lines 15-40; and Page 12, lines 16-
30; Page 16 table 2; Page 17, lines 26-31
and elsewhere throughout the original
claims and specification;

I. Rejections Under 35 U.S.C. §112 First Paragraph

The Examiner has rejected Claim 18 under 35 U.S.C. §112, first paragraph for failing to comply with the written description requirement. The Examiner is of the opinion that the meaning of the term "subset" is unclear.

Applicants have amended Claim 18 and removed the language "and subset thereof," as suggested by the Examiner.

II. Rejections Under 35 U.S.C. §112 Second Paragraph

The Examiner has rejected Claims 1-20 and 36 under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Examiner is of the opinion that Claims 1, 7, 11, 12, and 13 are vague.

Rejection of Claim 1: The Examiner has stated that Claim 1 is vague because:

"..it is not clear as to what level of saposin indicates the presence of lysosomal storage disorder. The claim is also not clear as to what levels of saposin are involved in the monitoring of the lysosomal storage disorder. The claim is also not clear as to what level of saposin and /or which saposin is correlated to each of the lysosomal storage disorders."

In response, Applicants submit that Claim 1 is not vague because the level of saposin that indicates the presence of a lysosomal storage disorder is anything different from the baseline level of the same protein as determined from levels that are present in about 95% of a control population unaffected by the lysosomal storage disorder.

Claim 1 has been amended to emphasize this distinction, as indicated above. Claim 1, as amended, contains the following limitation:

"determining a presence or extent of a lysosomal storage disorder when the first level is greater than the 95th percentile of the baseline level of the first saposin in the control population,"

The amended Claim 1 combines Claim 7 with original Claim 1 to indicate a specific first level (e.g. of saposins) needed to detect the presence or extent of a lysosomal storage disorder.

Furthermore, applicants have amended the claims to indicate:

"(ii) the similarity or difference of the first level compared to the baseline level is an indicator of presence or extent of the lysosomal storage disorder in the patient;"

Applicants have amended Claim 1 to include measuring a first level that corresponds to a saposin and the limitation of "comparing the first level to a baseline level."

Applicants respectfully submit that one of ordinary skill in the art would have been aware at the time of the invention that one common feature of LSDs is the accumulation and storage of materials within lysosomes. It was generally recognized that the accumulation and storage of material in the tissue of LSD affected individuals results in an increase in the number and the size of lysosomes within a cell from approximately 1% to as much as 50% of total cellular volume. Thus, in non-affected individuals, such materials are typically degraded into degradation products within the lysosome and then transported across the lysosomal membrane.

The specification describes how certain lysosomal proteins (e.g. lysosome-associated membrane proteins ("LAMPs"), saposins, and α -glucosidase) are present at elevated levels or depressed levels in the tissue lysosomes of affected individuals when compared to a control population (persons not having the disease) (See, Page 3, lines 20-34; Page 4, lines 12-34; Page 6, lines 12-22; and Page 7, lines 4-12). As is shown in Table 1, there is a strong positive correlation for the presence of at least one elevated level saposin and the presence an LSD's in an individual.

Applicants' invention describes a method that utilizes relative levels of these identified proteins biomarkers found, not in tissue but, in plasma, serum, whole blood, urine, or amniotic fluid samples for an early diagnosis of all LSD's. For example, sensitive immunoquantification assays have been developed to monitor the relative levels of useful biomarkers such as the lysosome-associated membrane proteins ("LAMPs"), saposins, and α -glucosidase when compared to baseline levels. The determination of relative levels of a saposin in an 'at-increased-risk' group of patients compared to individuals not having the disease will identify LSD affected individuals. This is especially relevant since 'at-increased-risk' patients need only supply a

blood or urine sample when compared to a brain or liver biopsy. Furthermore, one of ordinary skill in the art understands that it is not possible to extrapolate data from one tissue to another without at least confirmation experimentation, and more often than not, levels of specific proteins in one tissue is very different than another, as will be discussed in more detail below. In the present invention, one of ordinary skill in the art could not be reasonably expected to predict levels of a saposin in a non-tissue (e.g. plasma) from tissue data. Therefore, a method to identify and monitor a biomarker from blood or urine increases the reasonableness of diagnosing a specific LSD when compared to any tissue biopsy based diagnostic. Support can be found throughout the specification (e.g. Tables 1-5, Page 5, lines 24-30; Page 10, lines 7-20; and Page 11, lines 15-26), in particular, Pages 12-15 and Tables 1-5 of the specification.

Diagnosing a specific LSD using a single saposin from a blood or plasma sample would be difficult without Tables 1-5 indicating which biomarkers showed "strong positive" correlation (i.e. at least 80% of subjects with the disorder having a level of marker of at least a 95th percentile of a control population); a "positive" correlation (i.e. at least 40% of subjects with the disorder have a level of marker of at least the 95th percentile in a control population); no correlation; or a negative correlation. See Tables 1-5 and Pages 12-13 of the specification.

In contrast to the Examiner opinion on page 3 of the Office Action that:

"In line 6, the recitation of "similar or different" is vague and indefinite as to what level of saposin is determined."

Applicants respectfully submit that:

"...by examining the levels of several or all of the markers shown in a patient and comparing with the correlations shown in Table 1 or similar Table it is possible to classify a patient as having a particular disease or subset of diseases,..." as indicated on Page 13, lines 21-23 of Applicants specification.

Additionally, Page 19 lines 7-23, and Tables 1-5 discuss the saposin levels in the plasma of control and LSD-Affected individuals:

"To evaluate the suitability of each of the saposins as markers for new born screening for LSD, the levels of saposins A, B, C and D were determined in the plasma samples from 111 control

individuals (median age = 7, range =0-66) and 334 LSD affected individuals, representing 28 different disorders (Table 1)."

Applicants submit that the above paragraph and Tables 1-5 also addresses the Examiner concerns that the claims are not clear as to what level of saposin and/or which of the 4 saposin is correlated to each of the 30 lysosomal storage disorders.

Additionally, the Court has held that:

"The PTO has the burden of giving reason, supported by the record as a whole, why the specification is not enabling, and showing that the disclosure entails undue experimentation would be one way of meeting that burden." *In re Morehouse and Bolton*, 545 F.2d 162, 192 U.S.P.Q. 29, 31, 32 (C.C.P.A. 1976).

Applicants respectfully submit that the Examiner has NOT provided evidence to indicate that one of ordinary skill in the art would consider the terms "similar or different" as it is related to "relative" levels of a biomarker as vague and indefinite as to the level of saposin determined to have a strong or weak correlation with a specific LSD. This is especially true given the fact that detailed analysis are given in Tables 1-5 of the specification.

The Examiner has stated that parts (i) and (ii) of Claim 1 are further vague, and has requested Applicants to answer the following question:

"If the first level is similar to the base line level of the control population of patients unaffected by lysosomal storage disorder, how can the first level be an indicator of the presence or extent of the lysosomal storage disorder?"

Respectfully, Applicants have already given the answer on Page 14 lines 5-15 of the specification:

"If the measured level of an analyte does not differ significantly from baseline levels in a control population, the outcome of the diagnostic test is considered negative... For saposins and Lamp-1, a positive outcome is typically indicated by measured levels in excess of normal levels... The extent of departure between a measured value and a baseline value in a control population also provides an indicator of the probable accuracy of the diagnosis, and/or of the severity of the disease being suffered by the patient."

The Examiner is also of the opinion that Claim 7 is indefinite because it is not clear as to what the measured level that is greater than 95% level in the control population indicates. The Examiner has requested Applicants to answer the following question:

“Does it [measured level that is greater than 95% level] indicate the presence of the disorder?” [emphasis added]

Claim 7 is now canceled. However, Applicants direct the Examiner to amended Claim 1, which now contains the limitations of Claim 7. Namely:

“... determining a presence or extent of a lysosomal storage disorder when the first level is similar or different than the 95th percentile of the baseline level of the saposin in the control population;
wherein,

- (i) the similarity of the first level compared to the baseline level is an indicator of absence of the lysosomal storage disorder in the patient;*
- (ii) the difference of the first level compared to the baseline level is an indicator of presence or extent of the lysosomal storage disorder in the patient; ...”*

Thus, Applicants submit that that Claim 1 is not vague.

Rejection of Claim 11 and 12: The Examiner maintains that Claims 11 and 12 are vague because they are not clear as to what level of saposin indicates a progression of the disorder. The Examiner is also of the opinion that the claims are not clear as to what level of saposin and/or which of the 4 saposin is correlated to each of the 30 lysosomal storage disorders.

The court has held:

“One does not look to claims to find out how to practice the inventions they define, but rather, to the specification. *In re Rainer, Redding, Hitov, Sloan, and Stewart*, 305 F.2d 505, 134 U.S.P.Q 343, 346. (C.C.P.A. 1962).”

In response, Applicants direct the Examiner's attention to Page 19, lines 7-23, and Tables 1-5, which discuss the saposin levels and clarify which of the 4 saposin proteins are correlated to each of the 28 lysosomal storage disorders.

"To evaluate the suitability of each of the saposins as markers for new born screening for LSD, the levels of saposins A, B, C and D were determined in the plasma samples from 111 control individuals (median age = 7, range =0-66) and 334 LSD affected individuals, representing 28 different disorders (Table 1)."

Applicants submit that Tables 1-5 are of sufficient detail for one of ordinary skill in the art to ascertain and correlate combinations of saposin protein levels to each of the LSD disorders.

Rejection of Claim 13: The Examiner has held that Claims 13 is vague because the recitation of "the second saposin" lacks antecedent support. The Claim is further vague because it does not further limit Claim 1, and Claim 1 further recites the saposins in Claim 13.

In response, Applicants have amended each of Claims 1 and 5 to include the limitations of Claim 13, and Claim 13 has been canceled. Each of Claim 1 and Claim 5, as amended, further limits the use of the terms "first" saposin and "second" saposin. For example, Claim 5 includes:

"...a second saposin in a second sample from the patient, wherein the first saposin and second saposin are the same, and the first and second samples are obtained at different times;.. "

Thus, Applicants submit that the claims are precise and definite enough to provide a clear-cut indication of the scope of the claimed subject matter in light of the specification.

Turning now to the merits of the claims, Applicant's invention provides a method of diagnosing or monitoring a lysosomal storage disorder from a sample in a patient by measuring a level of at least a one saposin in a sample obtained from the patient, wherein the level of saposin is similar or different from a baseline level of saposin determined in a control population of patients that are unaffected by the lysosomal storage disorder. Using the level of one or more saposins from an easily obtainable sample of plasma, serum, whole blood, urine, or amniotic fluid sample as an indicator of presence or extent of the lysosomal storage disorder in a patient is unique.

II. Rejections Under 35 U.S.C. §103(a)

A. Claims 1, 4, 7, 13-15, 17 and 18 stand rejected under 35 U.S.C. §103(a) over the O'Brien '1991 Reference in view of the Sano '1989 Reference.

Applicants submit that each of Claims 1, 4, 7, 13-15, 17, and 18 contains a limitation that distinguishes the samples used for a method of diagnosing or monitoring an LSD. This limitation is: plasma, serum, whole blood, urine, or amniotic fluid. This recited limitation is not disclosed or suggested in the O'Brien '1991 Reference, wherein the only samples mentioned are brain, liver and spleen. More specifically, measuring the saposin levels from a biopsy or repeated biopsies of a patient's brain, liver, or spleen, as illustrated in the O'Brien '1991 Reference, is not realistic or practical for a non-invasive diagnostic screening method.

The Examiner is of the opinion that because the Sano '1989 reference indicates that saposin are found in human blood and plasma, therefore, it would have been obvious to one of ordinary skill in the art combine the teaching of the O'Brien '1991 Reference and use blood or plasma as a method of detecting an LSD.

In response, Applicants have amended Claim 1, upon which Claims 15, 17, and 18 are dependant. Applicants have canceled Claims 7, 13, and 14.

The O'Brien '1991 Reference clearly demonstrates that three different tissues contain three different levels saposin proteins. For example, Figure 7, page 307 of the O'Brien '1991 Reference shows a graph of the accumulation and concentration of saposin A, B, C and D in three different tissues (i.e. Brain, Liver, and Spleen) of control patients and patients having different LSD's. More specifically, NO detectable levels of saposin A, B, C, or D were found in the brains and livers of patients having Gaucher disease. In contrast, the patients having Gaucher disease had the highest spleen concentrations of saposin proteins when compared with the spleens from controls or all of the other LSD patients.

Applicants submit that the knowledge of saposin proteins being found in the blood, as indicated in the Sano '1989 reference, is not a critical link that would allow one of ordinary skill in the art to develop a diagnostic assay for an LSD based upon relative levels of saposin proteins

in blood or plasma. Because the amount of saposin proteins can be variable in different tissues and in different LSD's conditions (e.g. as indicated in Figure 7 of the O'Brien '1991 Reference), it is unlikely that one of ordinary skill in the art would have been able to "predict" the alternating levels of the saposin proteins in plasma from control and LSD affected individuals, as indicated in Tables 1-2 of the specification.

According to the Manual of Patent Examining Procedure -(MPEP) §2143 there are three requirements for Prima Facie Obviousness:

- 1) Some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;
- 2) A reasonable expectation of success; and
- 3) Prior art reference (or references when combined) must each list or suggest all of the claim limitations.

Thus, the consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have reasonable likelihood of success, viewed in the light of the prior art. Both the suggestion and the expectation of success must be founded in the prior art, not the applicant's disclosure. In view of the data presented in the O'Brien '1991 Reference indicating that saposin protein levels are variable in different tissues, and the absence of LSD data indicating any specific saposin protein levels in plasma from the Sano '1989 Reference, one of ordinary skill in the art COULD NOT have predicted the relative levels of saposin proteins in the blood needed to diagnose or monitor any LSD conditions. At best, this experiment may be "obvious-to-try." However, "obvious-to-try", or "obvious-to-test" or "experiment" is not a proper standard of 35 U.S.C. §103. *In re Goodwin*, 198 U.S.P.Q. 1,3 (C.C.P.A. 1978); *In re Antonie*, 195 U.S.P.Q. 6,8 (C.C.P.A. 1977); *In re Geiger*, 2 U.S.P.Q. 2d 1276, 1278 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1532 (Fed. Cir 1988). In fact, the mere need for experimentation to determine parameters needed to make an invention work is an application of the often rejected "obvious-to-try" standard and falls short of the statutory obviousness of 35 U.S.C §103. The

inability of an expert to predict that results obtainable with a claimed product suggests non-obviousness, not routine experimentation. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q. 2d 1434, 1440 (Fed. Cir. 1988).

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). The O'Brien '1991 Reference, indicates that the level of each of the saposin proteins in brain, liver, and spleen are present at different levels between tissues. The O'Brien '1991 Reference, also indicates that the level of each of the saposin proteins varies depending upon the type of LSD present in each patient. Additionally, the O'Brien '1991 Reference indicates control patients have relatively low levels of saposin proteins in all of the tissues studied. There is NO indication or suggestion that accumulation of saposin proteins in blood, plasma, or any other tissue from patients having an LSD would follow a predictable concentration pattern.

The Sano '1989 Reference, DOES NOT indicate, suggest, or even mention the levels of saposin proteins from LSD patients. NEITHER the suggestion NOR an expectation of successfully predicting that various saposin levels in blood or plasma show strong or weak correlations (as shown in Tables 1-5 of the Applicants specification) in patients having various LSD conditions can be found in the prior art.

Applicants submit that combining the cited references DOES NOT suggest a reasonable expectation of success for diagnosing or monitoring a LSD using blood or plasma from a patient.

Thus, Claims 1, 4, 15, 17 and 18 cannot be considered to be "obvious" over the O'Brien '1991 Reference in view of the Sano '1989 Reference under U.S.C. 35 §103(a).

B. Claims 5, 6, 9-12, 19, 20, and 36 stand rejected under 35 U.S.C. §103(a) over the O'Brien '1991 Reference in view of the Sano '1989 Reference, in further view of the U.S. Patent No.: 6,376,236 issued to Dubensky ("the '236 Patent").

The Examiner is of the opinion that the '236 Patent teaches that patients can undergo responsive treatments for lysosomal disorders and when combined together with the O'Brien

'1991 Reference and the Sano '1989 Reference, and it would have been obvious to monitor LSD's.

As discussed above, the combination of both the O'Brien '1991 Reference and the Sano '1989 Reference falls short of rendering the present invention as being obvious.

Applicants further submit that the '236 Patent teaches a recombinant alphavirus particle. Although the '236 Patent mentions that a specific aplphavirus may help with the treatment of Gaucher's disease, the term "saposin" is not even used throughout the 141 page document. Additionally, there is NO mention of utilizing or correlating blood or plasma saposin proteins to diagnose or monitor an LSD.

The courts have held that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Applicants submit that the combined O'Brien '1991 Reference and Sano '1989 Reference **DOES NOT** suggest a reasonable expectation of success for diagnosing or monitoring a LSD using blood or plasma from a patient, as described above. Applicants submit that data of saposin levels obtained with brain, liver and spleen CANNOT be extrapolated to blood. Additionally, the '236 Patent does not bridge this gap by disclosing a recombinant alphavirus particle that is used to treat one specific LSD (i.e. Gaucher Disease). Furthermore, since the '236 Patent does not even mention the terms saposin, blood, or plasma in the context of a diagnostic assay one of ordinary skill in the art **COULD NOT** be motivated to combine the references to obtain the Applicants invention as described in Claims 5, 6, 9-12, 19, 20, and 36.

Thus, Claims 5, 6, 9-12, 19, 20, and 36 cannot be considered to be "obvious" over the O'Brien '1991 Reference in view of the Sona '1989 Reference, further in view of the '236 Patent under U.S.C. 35 §103(a).

C. Claim 16 stand rejected under 35 U.S.C. §103(a) over the O'Brien '1991 Reference in view of the Sano '1989 Reference in further view of the Stastny '1992 Reference.

The Examiner is of the opinion that the O'Brien '1991 Reference and the Sano '1989 Reference disclose the invention substantially as claimed, except for the antibody being a monoclonal antibody. The Examiner is also of the opinion that since the Stastny '1992 Reference discloses a monoclonal antibody that reacts with saposin C, it would have been obvious to use this monoclonal antibody in the method taught by O'Brien '1991 in view of Sano in order to detect the level of saposin C.

As discussed above, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The rejection of Claim 16 is respectfully traversed for the reasons listed above for the O'Brien '1991 Reference and the Sano '1989 Reference. Applicants submit that results obtained with brain, liver and spleen CANNOT be extrapolated to blood. Additionally, the Stastny '1992 Reference DOES NOT bridge this gap by disclosing a monoclonal antibody with a high specificity to saposin C.

Applicants submit that combining the O'Brien '1991 Reference, the Sano '1989 Reference, and the Stastny '1992 Reference DOES NOT suggest a reasonable expectation of success for diagnosing or monitoring a LSD using blood or plasma from a patient, as described above. Thus, Claim 16 cannot be considered to be "obvious" under U.S.C. 35 §103(a).

RESPONSE TO EXAMINER'S RESPONSE TO ARGUMENTS

The Examiner is of the opinion that Applicants' previous arguments were not persuasive and did not overcome the §112, §102, and §103 rejections that the Examiner raised in the previous office action. As such, the Examiner presented the same arguments that were used in the previous Office Action. Namely, the O'Brien '1991 Reference, the Sano '1989 Reference to

principally were used to reject all of the Applicants' claims. In particular, the Examiner was drawn to Figure 7 on page 307 of the O'Brien '1991 Reference, and the teaching of the Sano '1989 Reference indicating that saposins were found in blood as evidence that one of ordinary skill in the art would have a reasonable expectation of success for diagnosing or monitoring a lysosomal storage disorder using blood or plasma samples from a patient.

In response, Applicants have reproduced Figure 7 from the O'Brian '1991 Reference below in order to underscore the unpredictability of determining concentrations of Saposins in different tissues and different disease states:

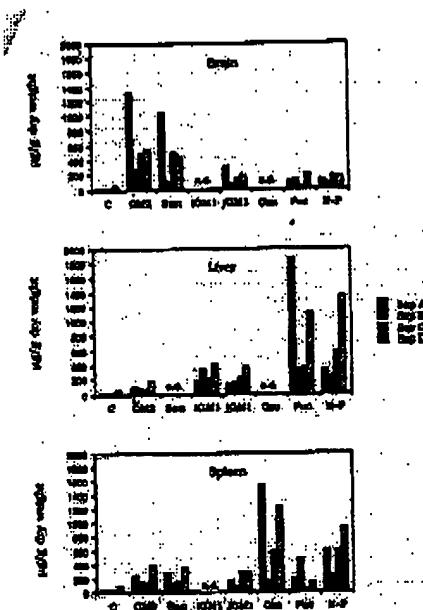


Figure 7. Accumulation of gamma-1 in lymphocytic storage disease. Concentration of gamma-1, N.P., and GM1 ganglioside in early dry weight. In the three disease conditions, GM1, ganglioside GM1, juvenile GM1 gangliosidosis, GM1, and Gaucher disease (type II), the hexoseamine-N-P, sulfatide Mannosidase disease (type A), D.L.D., not determined.

As shown, the level of Saposin A ("Sap A") varies dramatically in brain, liver, and spleen from patients having Sandhoff disease ("San"). For example, control levels of Saposin A and Saposin B in the brain, liver, and spleen were below 50 ug/g of dry weight of tissue. In contrast, the level of Saposin A in the brain was determined to be about 1400 ug/g of dry weight of tissue, and the level of Saposin B in the brain was determined to be about 100 ug/g of dry weight. Similarly, the level of Saposin A in the spleen was determined to be about 300 ug/g of dry

weight of tissue, and the level of Saposin B in the spleen was determined to be about 150 ug/g of dry weight.

The Examiner has held that given the O'Brian '1991 Reference and the Sano '1989 Reference:

"one of ordinary skill in the art would have a reasonable expectation of success for diagnosing or monitoring a lysosomal storage disorder using blood or plasma samples from a patient,"

However, Applicants submit that the Examiner's reasoning does not even hold true within a tissue comparison using the O'Brian '1991 Reference. For example, there were NO detectable levels of saposin A or saposin B in the liver of patients having Sandhoff's disease. How would one of ordinary skill in the art have a reasonable expectation of success of diagnosing or monitoring a lysosomal storage disorder (i.e. Sandhoff disease) with liver samples from a patient, using brain and spleen data? As shown in Table 2, page 20 of Applicants specification, the level of saposin A was about 33 ug/L and saposin B levels were about 71 ug/L in plasma from Sandhoff's disease. Applicants submit that saposin levels are highly variable when using cross tissue comparisons, and even more variable when using samples from patients having specific lysosomal storage disorders. The courts have held that:

In an area of technology shown to be highly unpredictable in process values, the discovery of optimum values not in anyway suggested by the prior art is more likely to be unobvious than obvious within the meaning of 35 USC §103.
In re Sebek, 465 F2d. 904, 175 U.S.P.Q. 93, 95 (C.C.P.A. 1972).

Thus, Applicants submit that that one of ordinary skill in the art could NOT predict the relative levels of saposins A, B, C, or D in plasma without having a first determined levels in both control subjects and patients having an LSD, as was completed in Applicants' application. Applicants' submit that the Examiner has NOT presented any references that indicate saposin levels in plasma or blood from patients having LSD. As such, one of ordinary skill in the art **COULD NOT** be motivated to combine any of the references to obtain the Applicants invention as described in Claims 1, 4-6, 8-12, 15-20, 36, and 39.

CONCLUSION

Applicants respectfully submit that, in light of the foregoing Amendments and comments, Claims 1, 4-6, 8-12, 15-20, 36, and 39 are all in condition for allowance. A Notice of Allowance is therefore requested for all claims. If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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